REMARKS

Following entry of the above amendments to the claims, claims 27-33, 36 and 40-65 are pending.

As required by 37 C.F.R. 1.121, a "marked-up" copy of the amendments to the claims is appended to this Amendment.

Support for the amendments to claim 27 is found at page 3, lines 12-14 ("at least 60 % homologous ...") and at page 11, lines 3-4 ("is useful in the treatment of ulcers").

Support for added claims 42-65 is found at page 5, line 29 to page 6, line 18 (claims 42-55), at page 3, lines 24-26 (claims 56-59), and in claims 28-33 (claims 60-65).

Rejection Under 35 USC §112, first paragraph

A. The Examiner maintained the rejection of claims 27-33 and 36 as containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (page 2 of Office Action). In particular, the Examiner asserted that 1) the configuration of the six disulfide bonds set forth in the claims is a minimal structural limitation because "this configuration sets forth only 12 of a possible 106 residues" and 2) the limitation "high stringency conditions" does not add meaningful structural limitations to the claimed invention because i) the present claims do not require that the homolog have a specific activity or function; ii) the present application contains no examples wherein the complement of SEQ ID NO 2 was used under any hybridization conditions for the isolation of cDNAs that were expressed and were shown to encode proteins with spasmolytic activity and iii) specific hybridization conditions were not set forth in the claims.

Applicants respectfully traverse this rejection.

First, Applicants note that claims 40-41 and newly added claims 60-65 are directed to a glycosylated polypeptide having an amino acid sequence according to SEQ ID NO:1 and that newly added claims 43-57 place further structural limitations on the homologue amino acid

sequence of claim 27, with claims 53-55, 57 and 59 in particular, limiting the homologue amino acid sequence to a sequence that differs from SEQ ID NO:1 by only one or two amino acids.

Second, Applicants note that in claim 27 as amended herein, the homologues of SEQ ID NO 1 must 1) be in N-glycosylated form and be useful in the treatment of ulcers, 2) have six disulphide bonds that form two trefoil domains, where the 12 cysteines that form the six disulphide bonds are in the configuration 1-5, 2-4, 3-6, 7-11, 8-10 and 9-12, and 3) be encoded by a nucleic acid sequence that is at least 60% homologous with a nucleic acid sequence that encodes SEQ ID NO:1 and that hybridizes under high stringency conditions to the nucleic acid sequence that encodes SEQ ID NO:1. Thus, in considering whether meaningful structural and functional limitations are placed on the polypeptides of claim 27, it is Applicants' position that one must consider whether all of the above limitations, taken together and not individually, place meaningful limitations on the claimed polypeptides.

For the reasons set forth below, it is Applicants' position that the above functional and structural requirements place the claims in compliance with the written description requirement of §112, first paragraph.

Regarding the Examiner's assertion that the configuration of the six disulfide bonds set forth in the claims is a minimal structural limitation because "this configuration sets forth only 12 of a possible 106 residues", Applicants submit that this is an unduly narrow view of this limitation. Claim 27 sets forth the required linkage of the six disulfide bonds and it is these specific linkages that enables the homologue amino acid sequence to assume the three dimensional structure characteristic of the two trefoil domains, where the presence of the two trefoil domains in the claimed homologues provides a common structural attribute that serves to distinguished the claimed homologues from other polypeptides.

Turning to the Examiner's remarks regarding the limitation "high stringency conditions", Applicants note as an initial matter that claim 27 has been amended to recite inter alia that the homologues of SEQ ID NO:1 1) have a specific function and 2) that they be encoded by a nucleic acid sequence that is at least 60% homologous with a nucleic acid sequence that encodes SEQ ID NO:1 and that hybridizes under high stringency conditions to the nucleic acid sequence that encodes SEQ ID NO:1. invention.

Finally, regarding the Examiner's assertion that Example 9 of the written description guidelines is not relevant to the present claims because the present application contains no

examples wherein the complement of SEQ ID NO 2 was used under any hybridization conditions for the isolation of cDNAs that were expressed and were shown to encode proteins with spasmolytic activity and specific hybridization conditions were not set forth in the claims (Example 9 reciting 65C and 6X SSC) , Applicants respectfully submit that there is no requirement for an application to contain any working examples and that the specification discloses that the term "homologue" indicates "a polypeptide encoded by DNA which hybridizes to the same probe as the DNA coding for HSP under conditions of high or low stringency (eg as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989)" (page 3, lines 5-11 of application) where the attached pages 9.47-9.51 from the 1989 edition of Sambrook et al disclose how to calculate the T_m of the hybrid formed between a probe and its target (paragraph 11 on pages 9.50-9.51) and state that "hybridizations are usually carried out in solutions of high ionic strength (6X SSC or 6X SSPE) at a temperature that is 20-25 C below the melting temperature (T_m)" (paragraph 8 on page 9.50).

Thus, in view of the teachings in the specification and the knowledge in the art, it is Applicants' position that one skilled in the art would recognize that the inventors in the present application were in possession of the claimed invention at the time of filing of the present application.

B. Claims 27-33, 36, 40 and 41 were rejected under section 112, first paragraph as being nonenabled because the specification "lacks guidance for making, and working examples of, a polypeptide or homolog with spasmolytic activity" (page 6 of Office Action) the claims do not place a functional limitation on the homologs of SEQ ID NO 1. In addition, the Examiner cited to articles by Bowie and Ngo as evidence that predicting structure and function from primary amino acid sequence data is extremely complex and that there does not exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence. The Examiner therefore concluded that in view of the above and in view of the breadth of the claims, it would require undue experimentation to make and/or use the full scope of the invention.

With all due respect, Applicants disagree.

First, Applicants submit that the amendments to claim 27 presented herein make clear that a functional limitation (useful in the treatment of ulcers) is placed on both the polypeptide of SEQ ID NO:1 and the homologues thereof. In addition, the application clearly teaches how to make a protein (the polypeptide of SEQ ID NO:1) useful in the treatment of peptic ulcers [see page 11, lines 3-4 and the Example of the application and Playford et al., Gastroenterology (1995), 108(1): 108-116, copy previously provided by Applicants, which shows that in the indomethacin/restraint model of gastric injury associated with peptic ulcers, glycosylated hSP decreased gastric damage (see discussion of Study 3 on pages 112-113, Fig. 5, and the first paragraph of page 115)].

Second, Applicants again note that claims 40-41 and newly added claims 60-65 are directed to a glycosylated polypeptide having an amino acid sequence according to SEQ ID NO:1 and that newly added claims 43-57 place further structural limitations on the homologue amino acid sequence of claim 27, with claims 53-55, 57 and 59 in particular, limiting the homologue amino acid sequence to a sequence that differs from SEQ ID NO:1 by only one or two amino acids.

Finally, in response to the Examiner's assertion that predicting structure and function from amino acid sequence is complex, Applicants submit that a careful reading of Bowie reveals that this reference is directed towards an analysis of the tolerance of an amino acid sequence towards change and sets forth two main approaches (natural selection or genetic engineering) to studying tolerance to sequence variation (paragraph bridging the left and right hand columns of page 1306 of Bowie). In particular, the authors of Bowie conclude that "studies in which these methods were used have revealed that proteins are surprisingly tolerant of amino acid substitutions" (first full paragraph of right hand column of page 1306) and they cite as an example studies with the lac repressor which showed that about one-half of the approximately 1500 substitutions studied at 142 positions in the lac repressor were phenotypically silent. In this regard, Applicants note that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine [In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]and that in claim 27 as amended herein, the homologues of SEQ ID NO 1 must 1) be in N-glycosylated form and be useful in the treatment of ulcers, 2) have six disulphide bonds that form two trefoil domains, where the 12 cysteines that form the six disulphide bonds are in the configuration 1-5, 2-4, 3-6, 7-11, 8-10 and 9-12, and 3) be encoded by a nucleic acid sequence that is at least 60%

homologous with a nucleic acid sequence that encodes SEQ ID NO:1 and that hybridizes under high stringency conditions to the nucleic acid sequence that encodes SEQ ID NO:1.

Accordingly, in view of the above arguments and the amendments to claim 27 and the added claims presented herein, Applicants submit that the pending claims are fully enabled by the present specification and withdrawal of this rejection is therefore respectfully requested.

Rejections Under 35 U.S.C. 112, second paragraph

The Examiner rejected claims 27-33 and 36 as indefinite over the use of the term "high stringency conditions" and "homologue" and because it is unclear if applicants are claiming a homolog of SEQ ID NO 1 or if the claimed polypeptide comprises a homolog of SEQ ID NO: 1.

Applicants respectfully traverse these rejections and address each in turn.

A. With respect to "high stringency conditions", the Examiner asserts that the specification fails to provide a definition of "high stringency conditions" and that while the applicant refers to pages of Sambrook as apprising one of ordinary skill in the art of the metes and bounds of the invention, such pages were not attached.

In reply, Applicants note that the specification in disclosing the term "high stringency conditions" refers to Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY , 1989 (page 3, lines 5-11 of application), a well known handbook of molecular biology. Applicants resubmit herewith pages 9.47 to pages 9.51 of the above edition of Sambrook and direct the Examiner's attention to paragraph 11 on pages 9.50-9.51 which discloses how to calculate the T_m of the hybrid formed between a probe and its target and to paragraph 8 on page 9.50 which states that "hybridizations are usually carried out in solutions of high ionic strength (6X SSC or 6X SSPE) at a temperature that is 20-25 C below the melting temperature (T_m)". Accordingly, Applicants submit that the phrase "high stringency conditions" would have a clear and definite meaning to one of skill in the art.

B. The Examiner asserts that the term "homologue" is indefinite because "the additional limitations, as discussed above, are indefinite" (page 4 of Office Action).

As the "additional limitations" discussed above as indefinite were "high stringency conditions", Applicants submit that this rejection is rendered moot by the arguments presented above in part A of Applicants' response to the section 112, second paragraph rejections.

C. In response to the Examiner's concern that it is unclear if applicants are claiming a homolog of SEQ ID NO 1 or if the claimed polypeptide comprises a homolog of SEQ ID NO: 1, Applicants submit that the amendment to claim 27 presented herein makes clear that Applicants are claiming a polypeptide which is SEQ ID NO 1 or a homolog of SEQ ID NO 1.

Accordingly, in view of the above amendments and remarks, withdrawal of the rejections under 35 U.S.C. 112, second paragraph is respectfully requested.

Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 27-33 and 36 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 10-13 of US Patent No. 5,783,416.

In reply, Applicants submit that they will submit an appropriate terminal disclaimer to obviate this rejection upon indication of allowable subject matter by the Examiner.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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Richard W. Bork

Richard W. Bork, Reg. No. 36,459
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

"Marked-Up" Version Of Amendments To The Claims

27. (Twice Amended) An isolated [human spasmolytic] polypeptide which is in N-glycosylated form and is useful in the treatment of ulcers, said polypeptide having an amino acid sequence according to SEQ ID NO:1

Glu Lys Pro Ser Pro Cys Gln Cys Ser Arg Leu Ser Pro His Asn Arg Thr Asn Cys Gly Phe Pro Gly Ile Thr Ser Asp Gln Cys Phe Asp Asn Gly Cys Cys Phe Asp Ser Ser Val Thr Gly Val Pro Trp Cys Phe His Pro Leu Pro Lys Gln Glu Ser Asp Gln Cys Val Met Glu Val Ser Asp Arg Arg Asn Cys Gly Tyr Pro Gly Ile Ser Pro Glu Glu Cys Ala Ser Arg Lys Cys Cys Phe Ser Asn Phe Ile Phe Glu Val Pro Trp Cys Phe Phe Pro Asn Ser Val Glu Asp Cys His Tyr

or an amino acid sequence that is a homologue [thereof that] of SEQ ID NO: 1 where the sequence of said homologue

A) has six disulphide bonds that form two trefoil domains, where the 12 cysteines that form the six disulphide bonds are in the configuration 1-5, 2-4, 3-6, 7-11, 8-10 and 9-12, and

B) is encoded by a nucleic acid sequence that is at least 60 % homologous to a nucleic acid sequence that encodes SEQ ID NO:1 and that hybridizes under high stringency conditions to [a] the nucleic acid sequence that encodes SEQ ID NO:1[,

wherein said polypeptide is characterized by being in N-glycosylated form and having spasmolytic activity].